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Citation for published version:

Song, P, Fang, Z, Wang, H, Cai, Y, Rahimi, K, Zhu, Y, Fowkes, FGR, Fowkes, FJI & Rudan, I 2020, 'Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study', *The Lancet Global Health*, vol. 8, no. 5, pp. e721-e729.
[https://doi.org/10.1016/S2214-109X\(20\)30117-0](https://doi.org/10.1016/S2214-109X(20)30117-0)

Digital Object Identifier (DOI):

[10.1016/S2214-109X\(20\)30117-0](https://doi.org/10.1016/S2214-109X(20)30117-0)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

The Lancet Global Health

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**Global and regional prevalence, burden and risk factors for carotid atherosclerosis:
a systematic review and modelling analysis**

Peige Song, PhD ^{1,2}, Zhe Fang, MD ³, Hanyu Wang, BA ⁴, Yutong Cai, PhD ⁵, Kazem Rahimi, DM ⁵, Yajie Zhu, PhD ⁵, F. Gerald R. Fowkes, PhD ¹, Freya J. I. Fowkes, DPhil ⁶, Igor Rudan, PhD ¹

¹ Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

² Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

³ Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts, US

⁴ School of Health Humanities, Peking University, Beijing, China

⁵ The George Institute for Global Health, University of Oxford, Oxford, UK

⁶ Burnet Institute, Melbourne, Australia

Corresponding Author: Yajie Zhu, PhD, The George Institute for Global Health, University of Oxford, Oxford, OX1 2BQ, United Kingdom (yajie.zhu@georgeinstitute.ox.ac.uk).

Telephone number: +44(0)1865617201

Word count for text: 3488

Summary

Background

Estimation of the epidemiological burden of carotid atherosclerosis can serve as a basis for cardiovascular disease prevention and management. This study provides the first estimation on the prevalence, number of cases and risk factors for carotid atherosclerosis in the general population globally and regionally.

Methods

For this systematic review and analysis, we conducted a comprehensive literature search in PubMed, Medline, Embase, Global Health and China National Knowledge Infrastructure for articles published until May 2019. Population-based studies that quantified prevalence of carotid atherosclerosis by means of elevated carotid intima-media thickness (cIMT), carotid plaque (CP), and carotid stenosis (CS), in which elevated cIMT was defined as a cIMT ≥ 1.0 mm, CP as a focal cIMT ≥ 1.5 mm encroaching into the lumen or at least 0.5 mm or 50% compared to the surrounding cIMT values, and CS as $\geq 50\%$ stenosis. Age- and sex-specific prevalence rates of elevated cIMT, CP and CS were estimated. United Nations population data were used to generate the number of people affected from 2000 to 2020. Random-effects meta-analyses were performed to assess the effects of risk factors for elevated cIMT and CP. Regional numbers of people living with elevated cIMT and CP in 2015 were derived using a risk factors-based model.

Findings

59 articles were included in the systematic review and analysis. The prevalence of elevated cIMT, CP and CS increased consistently with age and was higher in males than in females. Overall, the global prevalence of elevated cIMT, CP and CS in people aged 30-79 years in 2020 was 27.62%, 21.13% and 1.50%, equivalent to 1066.70 million, 815.76 million and 57.79 million affected people respectively. Smoking, diabetes and

hypertension were common risk factors for elevated cIMT and CP. In 2015, Western Pacific Region had the most cases of elevated cIMT (317·62 million) and CP (240·77 million), whereas the African Region had the least cases of elevated cIMT (59·08 million) and the Eastern Mediterranean Region had the least CP cases (44·59 million).

Interpretation

This study highlights a substantial global burden of carotid atherosclerosis. Effective strategies are needed for primary prevention and management of carotid atherosclerosis. High-quality epidemiological investigations on carotid atherosclerosis are called for to better address the global burden of carotid atherosclerosis at finer levels.

Funding None.

Research in context

Evidence before this study

An up-to-date understanding of the burden of carotid atherosclerosis worldwide is imperative for developing effective strategies for primary prevention and management and informing stakeholders. However, no current estimation on the prevalence of carotid atherosclerosis is available at the global level.

Added value of this study

Based on 59 articles, we provided the first robust prevalence estimates of carotid atherosclerosis in the general population at both the global and regional levels. The prevalence of elevated carotid intima-media thickness (cIMT), carotid plaque (CP) and carotid stenosis (CS) increased with advanced age and was higher in males than in females. In 2020, the prevalence of elevated cIMT, CP and CS in people aged 30-79 years was 27·62%, 21·13% and 1·50%, translating to 1066·70 million, 815·76 million and 57·79 million cases respectively.

Implications of all the available evidence

Elevated cIMT and CP are common disorders in the general population. The large numbers of people living with CP and CS worldwide represent a considerable public health concern. This study is expected to prompt further epidemiological studies on carotid atherosclerosis.

Introduction

Cardiovascular disease (CVD) has become a leading cause of disability and premature mortality globally ¹⁻³. According to the Global Burden of Disease Study, CVD affected an estimated 422.7 million people and caused 17.9 million deaths worldwide in 2015, representing 31% of all global deaths ^{1, 4}. CVDs are not only diseases of high-income countries (HIC). In recent years the burden of CVD has grown disproportionately in low- and middle-income countries (LMIC), where over 80% of CVD deaths now occur ^{3, 5}. By 2030, approximately 23.6 million people are predicted to die from CVDs annually ⁶. The huge and still growing burden of CVDs on individuals, families and the health care system suggests an urgent need for research on atherosclerotic diseases and implementation of preventive measures.

Atherosclerosis, the main pathological process of most CVDs, may begin early in life and remain latent and asymptomatic for long periods before progressing into its advanced stages ^{7, 8}. Early detection of atherosclerosis in apparently healthy people has mainly focussed on peripheral arteries and carotid arteries ⁹. Using ultrasonography, carotid intima-media thickness (cIMT) can be non-invasively evaluated ^{10, 11}. According to the 2016 European Guidelines on cardiovascular disease prevention in clinical practice, a cIMT of ≥ 1.0 mm is generally considered to be abnormal ⁹. The Mannheim Carotid Intima-Media Thickness Consensus also suggested that advanced stages of atherosclerosis, including plaque, stenosis and occlusion, are indicators of cardiovascular risk ¹⁰. In 2010, de Weerd and colleagues established the global prevalence of moderate ($\geq 50\%$ stenosis) and severe ($\geq 70\%$ stenosis) carotid stenosis (CS) in asymptomatic people, by using systematic review, meta-regression and an individual participant data meta-analysis ^{12, 13}.

An up-to-date understanding of the burden of carotid atherosclerosis worldwide is imperative for developing effective strategies for primary prevention and management and informing stakeholders. However, no current estimates of the prevalence of carotid

atherosclerosis are available at the global level. To fill this gap in knowledge, we conducted a systematic review of epidemiological studies that reported the prevalence of carotid atherosclerosis in the general population and have included studies using different measures of disease. We aimed 1) to provide the age- and sex-specific prevalence of carotid atherosclerosis; 2) to establish the main risk factors for carotid atherosclerosis; 3) to estimate the global number of people living with carotid atherosclerosis from 2000 to 2020; 4) to generate the regional number of people affected by carotid atherosclerosis in 2015.

Methods

Search Strategy and Study Selection

A comprehensive literature search was independently performed by two investigators (ZF and HZ) from inception to 07 May 2019 covering all epidemiological studies that reported the prevalence of three carotid atherosclerotic disorders, namely elevated cIMT, carotid plaque (CP) and CS in the general population. Four bibliographic databases, including PubMed, Medline, Embase and Global Health, were explored using a combination of terms related to carotid atherosclerosis and those related to prevalence without restrictions on language or publication date (complete details of the search strategies are listed in the **appendix**, p 3).

In 2018, we conducted a study on the prevalence of carotid atherosclerosis in China through a systematic review and meta-analysis (the China Carotid Atherosclerosis Study), where epidemiological studies on the prevalence of elevated cIMT and CP in the general Chinese population were included¹⁴. For the present systematic review, we updated our previous search in the China Carotid Atherosclerosis Study using the largest Chinese bibliographic source - China National Knowledge Infrastructure (CNKI) until 08 May 2019. This updated search for Chinese literature was also restricted to epidemiological studies investigating the prevalence of elevated cIMT, CP and CS in the general Chinese

population. In addition, hand searches of reference lists from the included articles and review articles on the topic were also performed to identify additional eligible articles. This present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline¹⁵. The review protocol was registered online on PROSPERO a prior (CRD42019134709).

Two investigators (PS and YZ) independently reviewed abstracts and full-text articles using prespecified eligibility criteria. We sought articles that reported prevalence data on elevated cIMT, CP or CS and potential risk factors in the general population. To be included, studies must have bilaterally scanned carotid arteries using ultrasonography and defined elevated cIMT, CP or CS in a standardized manner according to the 2016 European Guidelines on cardiovascular disease prevention in clinical practice guideline, the Mannheim Carotid Intima-Media Thickness Consensus and previous studies, where elevated cIMT was defined as a cIMT ≥ 1.0 mm, CP as a focal cIMT ≥ 1.5 mm encroaching into the lumen or at least 0.5 mm or 50% compared to the surrounding cIMT values, CS as $\geq 50\%$ stenosis, including occlusion^{9, 10, 14}. We excluded studies that were conducted in people who were not representative of the general population (e.g. people with specific diseases, individuals free from CVDs [asymptomatic individuals]). If multiple articles provided data from the same investigation, we included the one with the largest sample size.

Data Extraction and Quality Assessment

The following information from the included articles were independently extracted by two investigators (PS and YZ) from the included articles: first author, publication year, geographic location of investigation, regions of study location (African Region [AFR], Region of the Americas [AMR], South-East Asia Region [SEAR], European Region [EUR], Eastern Mediterranean Region [EMR] and Western Pacific Region [WPR], as designated by the World Health Organization [WHO]; HIC and LMIC, as designated by the World Bank

[WB]), study design, investigation date, sample size, average age of participants, proportion of female participants, diagnostic method, definition of disease (elevated cIMT, CP, or CS), number of cases. For articles where potential risk factors were explored using multivariable logistic regressions, the definitions of each risk factor and the reported odds ratio (OR) were also abstracted. In articles where the year of investigation was not specifically presented, we assigned it as five years, the mean time lag between investigation and publication based on articles with available data (**appendix**, pp 4–5), before the publication year.

To assess the quality of included articles, we employed a quality scale based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement¹⁶. The quality of each article was rated by two independent investigators (PS and YZ) on the basis of five modules: sample population, sample size, participation rate, outcome assessment, and analytical methods. Each module was assigned a score of 0-2, representing low-, moderate-, and high-quality respectively. The overall score represents the overall quality (**appendix**, p 6).

Any discrepancies at the bibliographic search, literature review and data extraction stages were resolved by consensus through discussion.

Statistical analysis

In the present study, the prevalence of elevated cIMT, CP and CS was estimated separately.

1) Epidemiological modelling of the prevalence of elevated cIMT, CP and CS

Multiple data points (age- and sex-specific prevalence) were generally provided in the included articles. To fully utilize the available information, we adopted a multilevel mixed-effects meta-regression^{17,18}. To control the effects of multiple data points from the same study and multiple studies from the same country, the study identification and country identification were added into the regression model as the random effect (u_i)¹⁹.

Given that:

$$\text{prevalence} = p = (\text{elevated cIMT /CP/CS cases})/(\text{number of participants})$$

Then, the prevalence was stabilized with the logit link,

$$\text{logit}(p) = \ln(p/[1 - p]) = \ln(\text{odds}) = \alpha + \beta_1 * x_1 + \beta_2 * x_2 + \dots + u_i$$

The effects of cluster-level variables $x_1 - x_n$, including age, female proportion, setting (rural, urban and mixed), income region (HIC and LMIC), investigation period (before 2000, 2000-2009, 2010 and after) due to availability of relevant information, were first assessed by a univariable meta-regression (**appendix**, pp 7-8). Age and female proportion were found to be significantly associated with the prevalence rates of elevated cIMT, CP and CS, therefore,

$$\text{logit}(p) = \alpha + \beta_1 * \text{Age} + \beta_2 * \text{Female proportion} + u_i$$

Then,

$$\begin{aligned} \text{prevalence} &= p \\ &= e^{(\alpha + \beta_1 * \text{Age} + \beta_2 * \text{Female proportion} + u_i)} / (1 + e^{(\alpha + \beta_1 * \text{Age} + \beta_2 * \text{Female proportion} + u_i)}) \end{aligned}$$

The age- and sex-specific prevalence of elevated cIMT, CP and CS was respectively estimated based on the above model.

2) Estimation of the global number of people with elevated cIMT, CP and CS from 2000 to 2020

The numbers of people living with elevated cIMT, CP and CS were respectively generated by multiplying the estimated age- and sex-specific prevalence rates by the corresponding world populations from 2000 to 2020, obtained from the United Nations Population Division (UNPD) ²⁰. To derive robust estimation, we restricted prevalence and number of cases to the age range 30-79 years, where most informative data points covered.

3) Meta-analysis of risk factors for elevated cIMT and CP

A subset of included articles additionally explored potential risk factors for elevated cIMT, CP and CS. Only risk factors that had been assessed in at least three investigations using multivariable logistic regressions were included for meta-analysis. A random-effects (DerSimonian and Laird method) meta-analysis was used to synthesize the effects of risk factors¹⁷. Due to data availability, this was only done for elevated cIMT and CP.

4) Estimation of the regional number of people with elevated cIMT and CP in 2015

In line with the China Carotid Atherosclerosis Study and our previous studies, three common risk factors for elevated cIMT and CP, including current smoking, hypertension and diabetes, were selected. to derive the regional number of people living with elevated cIMT and CP based on a risk-factor-based model^{14,21}. The latest prevalence data of current smoking (in 2015), hypertension (in 2015) and diabetes (in 2015) were obtained from the WHO report on the global tobacco epidemic and the WHO Global Health Observatory data repository^{26, 2728, 29}.

The study approach is demonstrated in the **appendix** (p 47). All analyses were performed with Stata, version 14.0 (StataCorp) and R, version 3.3.0 (R Foundation for Statistical Computing).

Results

The study selection process is summarized in **Figure 1**. Our initial literature search identified 8632 citations. After removal of duplicates and apparently irrelevant records, 515 articles were examined in full text. Finally, 59 articles covering 21 countries (the geographical locations are demonstrated in the **appendix**, p 48) fulfilled the inclusion criteria, among which 25 articles reported prevalence data on elevated cIMT, 34 on CP and 16 on CS. The characteristics of every study are shown in the **appendix** (pp 9–26).

The majority (n=45, 76.3%) of the included articles were published in the last decade (2010-2019), and more than half (n=34, 57.6%) were conducted in rural-urban mixed

settings. Moreover, 21 (35.6%) and 30(50.8%) of the included articles respectively provided age- and sex-specific prevalence rates. Almost half of the included articles (n=28, 47.5%) were conducted in HIC and the others (n=31, 52.5%) were in LMIC. All the 59 articles had a quality score of six or above. The detailed quality assessments are in the **appendix** (pp 27–28).

Based on the available data points from the included articles, the sex-specific relationships between age and the prevalence of elevated cIMT, CP and CS were demonstrated in **Figure 2**. Generally, the prevalence of elevated cIMT, CP and CS all rose with advanced age. The estimated age- and sex-specific prevalence of elevated cIMT, CP and CS is listed in **Table 1**. For elevated cIMT, CP and CS, females consistently had lower prevalence rates than males over the whole age span covered by available data points and of research interest (30-79 years). In 2020, the prevalence of elevated cIMT in people aged 30-79 years was 27.62% (95% CI=16.92-41.29; males: 32.12% [95% CI=20.17-46.72]; females: 23.18% [95% CI=13.71-35.93]), that of CP was 21.13% (95% CI=13.24-31.54; males: 25.18% [95% CI=16.13-36.69]; females: 17.12% [95% CI=10.39-26.46]) and that of CS was 1.50% (95% CI=1.08-2.10; males; 1.83% [95% CI=1.31-2.57]; females: 1.17% [95% CI=0.84-1.63]).

The numbers of people living with elevated cIMT, CP and CS in the years 2000 and 2020 were generated by applying the population data to the age- and sex-specific prevalence rates (**Table 2**). Due to demographic ageing during 2000-2020, the numbers of people with elevated cIMT, CP and CS increased by 57.49%, 58.97% and 59.13% respectively. For elevated cIMT, CP and CS, the age group where the increasing rate was the highest (at approximately 85%) was 50-59 years. In 2020, the cases of elevated cIMT, CP and CS worldwide were 1066.70 million (95%CI=653.30-1594.52), 815.76 million (95%CI=511.36-1217.93) and 57.79 million (95%CI=41.52-81.02) respectively.

We were able to evaluate the effects of seven factors for elevated cIMT, and nine factors for CP in a meta-analysis manner (**Table 3**). Advanced age, male sex, current smoking, diabetes, and hypertension were associated with a higher risk of elevated cIMT. For CP, the significant risk factors included male sex, former smoking, current smoking, diabetes, hypertension and a higher level of systolic blood pressure (SBP) and a lower level of high-density lipoprotein (HDL). The individual articles that contributed to those meta-analyses are listed in the **appendix** (pp 29–45).

The numbers of people affected by elevated cIMT and CP in the six WHO regions in 2015 were generated based on a “risk factor model” by taking into account the regional difference in the exposure to three major risk factors, namely current smoking, diabetes and hypertension (**appendix**, p 1). As shown in **Figure 3** and detailed in the **appendix** (p 46), WPR had the largest share of global cases of elevated cIMT (33.36%, 317.62 million [95% CI=194.71-473.73]) and CP cases (33.20%, 240.77 million [95% CI=150.96-359.22]). AFR had the least cases of elevated cIMT (6.21%, 59.08 million [95% CI=34.91-92.19]) whereas EMR had the smallest share of CP cases (6.15%, 44.59 million [95% CI=27.36-68.44]). The age groups that contributed the most cases of elevated cIMT and CP were 50-59 years for AFR, SEAR and EMR, and 60-69 years for AMR, EUR and WPR.

Discussion

This systematic review and meta-analysis comprehensively portrays the prevalence of elevated cIMT, CP and CS in the general population worldwide. We found that more than one in four individuals aged 30-79 years had an abnormal cIMT of 1.0 mm and above, translating to more than one billion affected people in 2020. In addition, more than one in five people aged 30-79 years had CP and 1.50% were affected by CS, equivalent to 816 million and 58 million cases in 2020. cIMT, CP and CS were more common in older than in younger people, and in males than in females. Current smoking, diabetes, and hypertension were confirmed as common risk factors for both elevated cIMT and CP. At

the regional level, WPR had around one-third of global cases of elevated cIMT and CP, whereas AFR had the least cases of elevated cIMT and EMR had the least CP cases in 2015, demonstrating substantial variations across the globe.

As revealed in our meta-regression, elevated cIMT, CP and CS become more common in older people, which reinforces the concept that atherosclerosis is a chronic disease process of the artery which manifests more commonly as people age ^{7, 8}. cIMT measures the structural changes in the carotid arterial walls, and an increased cIMT could be a marker of early-stage systemic atherosclerosis, as well as of smooth muscle hypertrophy or hyperplasia ⁹. In our study, we found that over one in four individuals aged 30-79 years had an elevated cIMT, defined as a cIMT ≥ 1.0 mm. Although a cIMT of 1.0 mm and greater is considered as abnormal, some elevated cIMT conditions are clinically benign and may not progress to cardiovascular events ^{9, 22, 23}. The 2016 European Guidelines on cardiovascular disease prevention in clinical practice does not recommend the implementation of cIMT measurements in daily clinical practice and routinely in cardiovascular risk assessment ⁹. The over one billion cases of elevated cIMT worldwide should not create unnecessary anxiety among stakeholders. Other advanced-stage phenotypes of carotid atherosclerosis, namely CP or CS, are correlated to elevated cIMT but reflect different predictive value for CVDs ²⁴⁻²⁶. Previous studies have suggested that people with CP or CS are at a higher risk of developing CVDs ^{10, 24, 27}. The systematic detection of CP has been recommended in assessing cardiovascular risk ⁹. Given the fact that atherosclerosis is a diffuse disease of arteries, people with carotid atherosclerosis are more likely to have atherosclerotic diseases in other arterial beds, such as peripheral artery disease and coronary heart disease ^{28, 29}. The large numbers of people living with CP and CS represent sizeable potential cardiovascular events and therefore a huge burden of diseases on the global health-care system ^{10, 27}.

In line with the meta-analysis by de Weerd and colleagues and previous investigations, our analysis also noted a clear male predominance in carotid atherosclerosis ^{12, 13, 30, 31}. This widely accepted cardiovascular advantage in females might be conferred by the protective role of, for example, oestrogens in endothelial function and lipid homeostasis ³²⁻³⁴. Smoking, diabetes and hypertension were revealed as significant factors for elevated cIMT and CP in our meta-analyses for risk factors, which agrees with previous epidemiological investigations ³⁵⁻³⁷. Early detection and management of diabetes and hypertension might help to slow the progression of atherosclerotic complications and much attention should be paid to subpopulations that are especially vulnerable, such as males, heavy smokers, people with established CVDs ⁹. For CP, we were able to identify the effects of both current smoking and former smoking, with the latter having a lower meta-OR. The difference between those two effects implies the potential benefits of smoking cessation in reducing the risk of CP ^{37, 38}. For CP, a lower level of HDL was found to be a significant risk factor, which agrees with previous evidence as revealed in a systematic review ³⁹. However, the association between elevated cIMT and the level of HDL was not assessed due to lack of relevant data, as was also the case with different lipids on elevated cIMT, CP and CS. More studies are still needed on the relationship between lipid profile and carotid atherosclerosis.

To the best of our knowledge, this study is the first to derive robust prevalence estimates of carotid atherosclerosis in the general population at both the global and regional levels, serving to inform policymakers of the epidemiological magnitude and profile of this public health issue. A special merit of this study is that we adopted the standardized definitions of carotid atherosclerosis, including elevated cIMT, CP and CS, before pooling prevalence estimates from different studies, which reduced the uncertainty of our estimation due to differing case definitions ⁹. Benefitting from a comprehensive search strategy and dual review process, we finally included a total of 59 articles for our modelling analysis. Sufficient data from the included articles enabled us to provide the

broadest research scope of the epidemiological distribution of elevated cIMT, CP and CS simultaneously. We successfully provided prevalence estimates of elevated cIMT, CP and CS by age and sex. In the effect assessments of potential risk factors, only factors that were reported based on multivariable logistic regressions were included. This strict inclusion criterion could help to avoid the suspected bias caused by univariable logistic regression²¹.

Our study has unavoidable limitations. The first crucial limitation is the deficiency of information on risk factors. For elevated cIMT, we were only able to explore the effects of seven potential risk factors and for CP only nine. The limited amount of information on risk factors for CS restricted our ability to conduct the risk factor assessment in a meta-analytic manner. Furthermore, the effects of many important risk factors or covariates of elevated cIMT, CP and CS, such as hypercholesterolemia, obesity and physical exercise were not able to be established. A second limitation was that in the distribution of regional cases, only demographic structures (age and sex) and the exposure levels of three risk factors (current smoking, diabetes and hypertension) in different geographic regions were accounted for based on a “risk factor-based model”. Previous studies have suggested that the prevalence of carotid atherosclerosis might be lower in Asians compared to their Western counterparts; however, we were not able to assess the possible ethnic disparity due to the limited availability of relevant information^{30, 40}. The effects of ethnicity, together with other potential drivers of disease, were not able to be taken into account in our modelling at the regional level, which might have resulted in partially biased prevalence for each geographic region. In addition, the lack of risk factor assessment for CS restricted our ability to estimate the regional prevalence of CS. Thirdly, none of the included articles was based on investigations in EMR, so that our prevalence estimates for EMR might not precisely reflect the real situation. To better explore the distributions of diseases at finer dimensions, the need to scale up high-quality data on the epidemiology

of carotid atherosclerosis, especially through prospective cross-national, studies using comparable definitions and assessments, is highlighted.

To conclude, this study demonstrates that elevated cIMT and CP are common disorders in the general population. The large number of people living with CP and CS may bring a considerable burden of CVDs and represents a major public health concern worldwide. Smoking, diabetes and hypertension are common risk factors for both elevated cIMT and CP. Around one-third of global cases of elevated cIMT and CP were in WPR in 2015. Given the prominent role of ageing as a risk factor for carotid atherosclerosis, a larger number of people affected by carotid atherosclerosis are expected in the context of global demographic ageing.

Contributors

PS and YZ planned the study and IR and PS designed the methods. PS, YZ, ZF and HW contributed to the literature review and PS and YZ extracted data. PS, YZ and IR conducted statistical analyses. PS prepared the first draft with important contributions from YC, KR, FJIF and FGFR. All authors interpreted results, commented on drafts of the paper and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

All data generated or analysed in this study are included in the appendix.

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Tables and Figures

Table 1. Estimated prevalence of elevated cIMT, CP and CS in people aged 30-79 years, by age group and sex

Age group	Elevated cIMT (%; 95% CI)		CP (%; 95% CI)		CS (%; 95% CI)	
	Male	Female	Male	Female	Male	Female
30-34 years	11.71 (5.96-21.74)	6.87 (3.40-13.38)	7.48 (4.04-13.45)	4.10 (2.18-7.60)	0.52 (0.28-0.96)	0.31 (0.17-0.57)
35-39 years	15.80 (8.25-28.12)	9.45 (4.76-17.87)	10.47 (5.74-18.34)	5.83 (3.12-10.62)	0.70 (0.41-1.20)	0.42 (0.25-0.72)
40-44 years	20.97 (11.32-35.55)	12.86 (6.63-23.47)	14.47 (8.10-24.50)	8.22 (4.46-14.66)	0.94 (0.58-1.50)	0.56 (0.35-0.89)
45-49 years	27.29 (15.33-43.77)	17.27 (9.14-30.21)	19.66 (11.32-31.93)	11.46 (6.33-19.89)	1.25 (0.84-1.88)	0.75 (0.50-1.12)
50-54 years	34.68 (20.41-52.37)	22.79 (12.48-37.94)	26.14 (15.59-40.41)	15.77 (8.90-26.41)	1.68 (1.19-2.37)	1.01 (0.72-1.42)
55-59 years	42.89 (26.64-60.85)	29.46 (16.79-46.35)	33.85 (21.08-49.51)	21.31 (12.39-34.16)	2.24 (1.66-3.01)	1.35 (1.00-1.81)
60-64 years	51.52 (33.93-68.74)	37.13 (22.21-55.00)	42.54 (27.87-58.65)	28.15 (16.98-42.87)	2.98 (2.29-3.88)	1.80 (1.38-2.35)
65-69 years	60.05 (42.05-75.69)	45.52 (28.74-63.38)	51.71 (35.85-67.23)	36.17 (22.82-52.05)	3.97 (3.07-5.10)	2.41 (1.86-3.11)
70-74 years	68.01 (50.60-81.52)	54.17 (36.28-71.04)	60.76 (44.69-74.80)	45.04 (29.95-61.10)	5.25 (4.03-6.83)	3.21 (2.44-4.20)
75-79 years	75.05 (59.10-86.22)	62.57 (44.54-77.68)	69.13 (53.87-81.12)	54.24 (38.20-69.45)	6.93 (5.15-9.26)	4.26 (3.13-5.77)
Overall (30-79 years) in 2020	32.12 (20.17-46.72)	23.18 (13.71-35.93)	25.18 (16.13-36.69)	17.12 (10.39-26.46)	1.83 (1.31-2.57)	1.17 (0.84-1.63)

Note: cIMT=carotid intima-media thickness; CP=carotid plaque; CS=carotid stenosis; CI=confidence interval.

Table 2. Estimated number of people with elevated cIMT, CP and CS worldwide from 2000 to 2020 and the rates of change

Age group	Elevated cIMT (million, 95% CI)		CP (million, 95% CI)		CS (million, 95% CI)		Relative rate of change (%, 2000-2020)		
	2000	2020	2000	2020	2000	2020	CAS	CP	CS
30-34 years	44.56 (22.45-84.20)	56.56 (28.50-106.86)	27.80 (14.92-50.50)	35.30 (18.94-64.11)	2.00 (1.08-3.68)	2.54 (1.38-4.68)	26.93	26.96	26.92
35-39 years	54.21 (27.96-98.73)	69.02 (35.60-125.70)	35.02 (19.05-62.20)	44.59 (24.25-79.20)	2.40 (1.40-4.11)	3.06 (1.78-5.24)	27.32	27.33	27.32
40-44 years	63.38 (33.64-110.54)	83.73 (44.44-146.03)	42.52 (23.55-73.37)	56.17 (31.11-96.92)	2.81 (1.76-4.48)	3.71 (2.32-5.92)	32.10	32.10	32.10
45-49 years	75.02 (41.21-124.50)	106.96 (58.76-177.52)	52.40 (29.71-87.23)	74.72 (42.37-124.38)	3.38 (2.26-5.05)	4.82 (3.22-7.20)	42.59	42.59	42.59
50-54 years	76.03 (43.50-119.47)	128.08 (73.30-201.23)	55.43 (32.38-88.38)	93.39 (54.57-148.89)	3.55 (2.51-5.01)	5.98 (4.24-8.44)	68.46	68.48	68.49
55-59 years	75.63 (45.38-112.12)	140.08 (84.06-207.63)	57.64 (34.96-87.47)	106.77 (64.76-162.00)	3.75 (2.78-5.04)	6.94 (5.16-9.33)	85.21	85.23	85.24
60-64 years	83.24 (52.64-116.37)	142.23 (89.96-198.78)	66.30 (42.02-95.35)	113.29 (71.81-162.91)	4.48 (3.44-5.84)	7.67 (5.88-9.98)	70.86	70.89	70.92
65-69 years	80.29 (53.69-106.05)	141.47 (94.66-186.78)	66.69 (44.42-90.77)	117.56 (78.33-159.93)	4.82 (3.73-6.21)	8.50 (6.58-10.95)	76.21	76.27	76.39
70-74 years	71.58 (50.64-89.78)	114.27 (80.94-143.18)	61.77 (43.36-79.72)	98.69 (69.36-127.23)	4.89 (3.74-6.38)	7.83 (5.99-10.22)	59.64	59.77	60.11
75-79 years	53.37 (39.84-63.99)	84.28 (63.10-100.83)	47.60 (35.21-58.52)	75.29 (55.87-92.35)	4.23 (3.13-5.68)	6.73 (4.98-9.05)	57.92	58.20	59.31
Overall (30-79 years)	677.32 (410.96-1025.74)	1066.70 (653.30-1594.52)	513.16 (319.58-773.52)	815.76 (511.36-1217.93)	36.32 (25.83-51.50)	57.79 (41.52-81.02)	57.49	58.97	59.13

Note: cIMT=carotid intima-media thickness; CP=carotid plaque; CS=carotid stenosis; CI=confidence interval.

Table 3. Synthesized effect size of risk factors for elevated cIMT and CP that were investigated in at least three studies using multivariate design

Risk factor	Number of studies	OR (95% CI)	z value	P value
Elevated cIMT				
Risk factor 1-Age (per 10-year increase)	4	2.71 (2.07-3.55)	7.26	<0.001
Risk factor 2-Female sex	5	0.49 (0.38-0.64)	5.43	<0.001
Risk factor 3-Current smoker	5	1.76 (1.34-2.30)	4.11	<0.001
Risk factor 4-Current alcohol drinker	3	0.94 (0.70-1.26)	0.41	0.680
Risk factor 5-Diabetes	4	2.23 (1.48-3.36)	3.82	<0.001
Risk factor 6-Hypertension	5	1.55 (1.03-2.34)	2.08	0.038
Risk factor 7-Dyslipidemia	3	0.90 (0.65-1.25)	0.61	0.542
CP				
Risk factor 1-Age (per 10-year increase)	4	1.79 (0.93-3.43)	1.76	0.079
Risk factor 2-Female sex	5	0.55 (0.33-0.94)	2.20	0.028
Risk factor 3-Former smoker	3	1.58 (1.06-2.36)	2.26	0.024
Risk factor 4-Current smoker	5	1.70 (1.41-2.04)	5.64	<0.001
Risk factor 5-Diabetes	3	1.45 (1.12-1.90)	2.77	0.006
Risk factor 6-Hypertension	3	1.75 (1.44-2.13)	5.56	<0.001
Risk factor 7-SBP (per 10 mmHg increase)	3	1.11 (1.08-1.15)	6.50	<0.001
Risk factor 8-HDL (per mmol/L increase)	3	0.46 (0.21-0.99)	1.98	0.048
Risk factor 9-BMI (per kg/m ² increase)	4	0.97 (0.91-1.02)	1.15	0.249

Note: cIMT=carotid intima-media thickness; CP=carotid plaque; OR=odds ratio; CI=confidence interval; SBP= Systolic Blood Pressure; HDL=high-density lipoprotein; BMI=body mass index; The definitions of some risk factors varied slightly across studies. ORs for binary variable risk factor indicated the risk of elevated cIMT/CP compared with those without the risk factor, except for current alcohol drinkers (vs never drinkers), former smokers (vs never smokers), current smokers (vs never smokers).

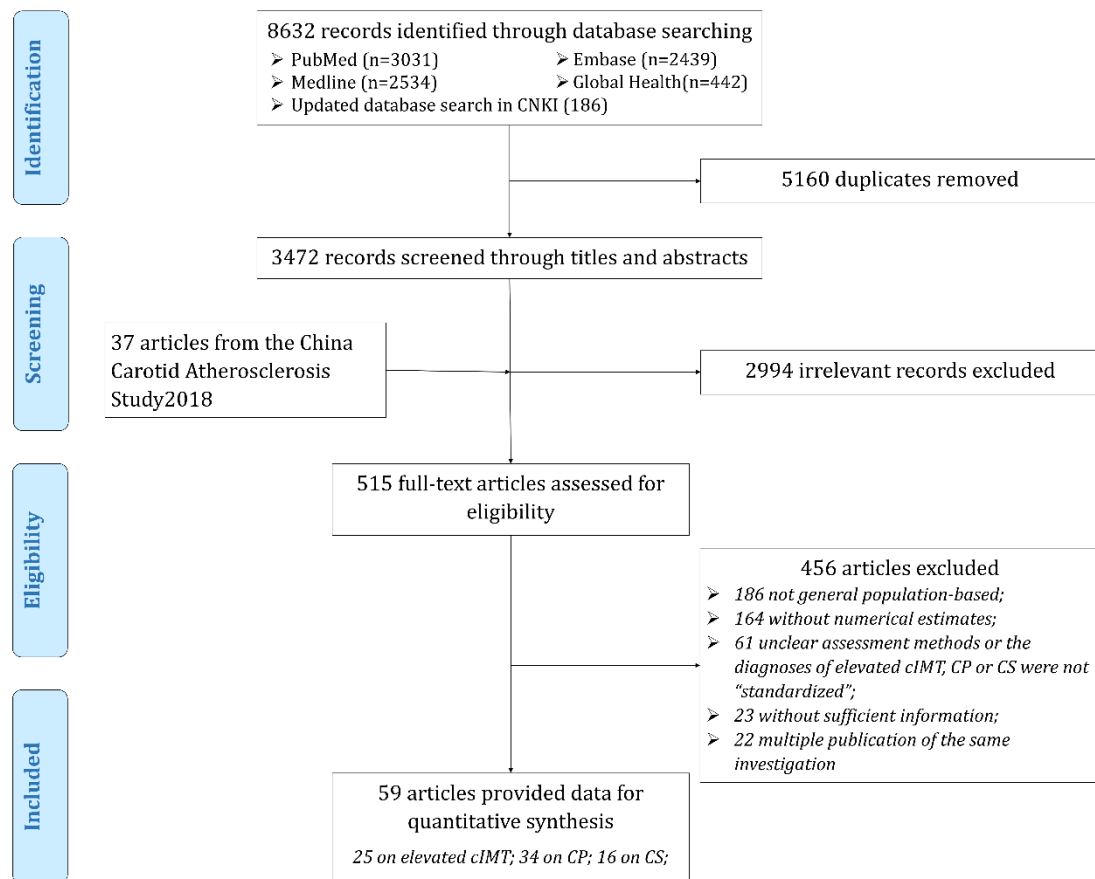


Figure 1. PRISMA diagram of study selection

Note: cIMT=carotid intima-media thickness; CP=carotid plaque; CS=carotid stenosis.

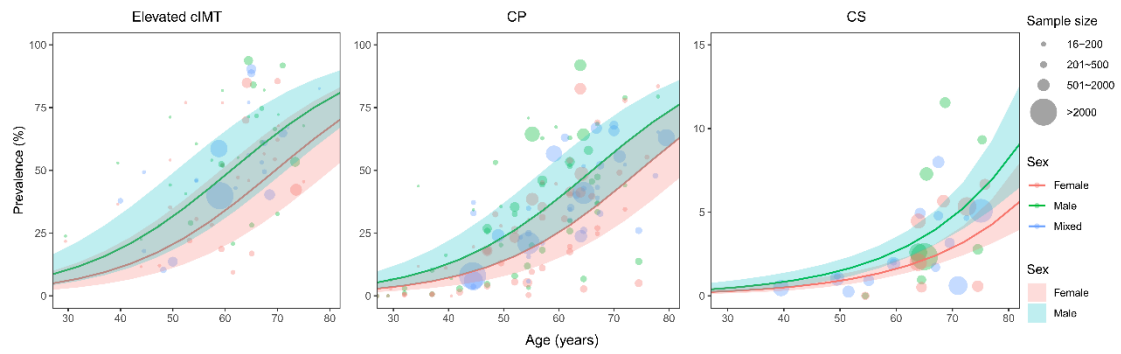


Figure 2. Age-and sex-specific prevalence of elevated cIMT, CP and CS, with 95% CI

Note: CI, confidence interval; cIMT=carotid intima-media thickness; CP=carotid plaque; CS=carotid stenosis; For elevated cIMT and CS, the regression lines at younger (<40 years) and older (>75 years) age groups are based on few data points or projection only; For CS, to make the plot readable, the study by Savji N, et al.(2013) was removed when drawing the plot due to its overwhelmingly large sample size influence.

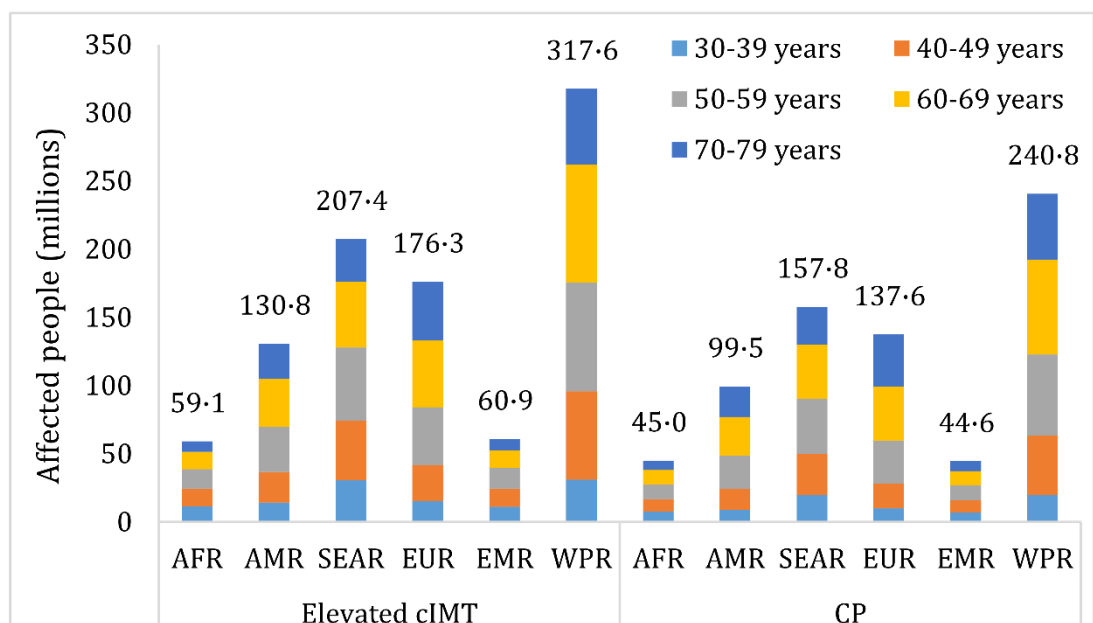


Figure 3. Regional number of people with elevated cIMT and CP and contributing age groups in 2015

Note: cIMT=carotid intima-media thickness; CP=carotid plaque; AFR= African Region; AMR= Region of the Americas; SEAR= South-East Asia Region; EUR= European Region; EMR= Eastern Mediterranean Region; WPR= Western Pacific Region; People with elevated cIMT and CP were restricted to those aged 30-79 years given the study context.